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US-PAT-NO: 6576235
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TITLE: PEG-urate oxidase conjugates and use thereof

DATE-ISSUED: June 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Saifer; Mark G. P.	San Carlos	CA		
Sherman; Merry R.	San Carlos	CA		

US-CL-CURRENT: 424/94.4; 435/189, 435/191, 435/252.3, 435/320.1, 530/350, 536/23.2

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CLAIMS:

What is claimed is:

1. A conjugate of uricase that retains at least about 75% of the uricolytic activity of unconjugated uricase and is substantially reduced in immunogenicity, comprising a purified uricase containing no more than about 10% non-tetrameric aggregated uricase, said purified uricase comprising subunits in which each subunit of the uricase is covalently linked to an average of 2 to 10 strands of PEG, wherein each molecule of PEG has a molecular weight between about 5.kDa and 100 kDa.

2. The conjugate of claim 1, wherein the uricase is mammalian uricase.

3. The conjugate of claim 2, wherein the uricase is porcine liver, bovine liver or ovine liver uricase.

4. The conjugate of claim 1, wherein the uricase is recombinant.

5. The conjugate of claim 4, wherein the uricase has the sequence of porcine, bovine, ovine or baboon liver uricase.

6. The conjugate of claim 4, wherein the uricase is chimeric.

7. The conjugate of claim 6, wherein the chimeric uricase contains portions of porcine liver and baboon liver uricase.

8. The conjugate of claim 7, wherein the chimeric uricase is pig-baboon chimeric uricase (PBC uricase).

9. The conjugate of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:1 has been replaced by lysine (R291K) and threonine residue 301 of SEQ ID NO:1 has been replaced by serine (T301S) (PKS uricase).

10. The conjugate of claim 4, wherein the uricase has the sequence of baboon liver uricase (SEQ ID NO:2) in which tyrosine 97 has been replaced by histidine.

11. The conjugate of claim 4, wherein the uricase comprises an amino terminus and a carboxy terminus, and wherein the uricase is truncated at one terminus or both termini.

12. The conjugate of claim 1, wherein the uricase is a fungal or microbial uricase.

13. The conjugate of claim 12, wherein the fungal or microbial uricase is isolated from Apergillus flavus, Arthrobacter globiformis or Candida utilis, or is a recombinant enzyme having the sequence of one of those uricases.

14. The conjugate of claim 1, wherein the uricase is an invertebrate uricase.

15. The conjugate of claim 14, wherein the invertebrate uricase is isolated from Drosophila melanogaster or Drosophila pseudoobscura, or is a recombinant enzyme having the sequence of one of those uricases.

16. The conjugate of claim 1, wherein the uricase is a plant uricase.

17. The conjugate of claim 16, wherein the plant uricase is isolated from root nodules of Glycine max or is a recombinant enzyme having the sequence of that uricase.

18. The conjugate of claim 1, wherein the PEG has an average molecular weight between about 10 kDa and 60 kDa.

19. The conjugate of claim 18, wherein the PEG has an average molecular weight between about 20 kDa and 40 kDa.

20. The conjugate of claim 1, wherein the average number of covalently coupled strands of PEG is 3 to 8 strands per uricase subunit.

21. The conjugate of claim 20, wherein the average number of covalently coupled strands of PEG is 4 to 6 strands per uricase subunit.

22. The conjugate of claim 1, wherein the uricase is tetrameric.

23. The conjugate of claim 1, wherein the strands of PEG are covalently coupled to uricase via linkages selected from the group consisting of urethane linkages, secondary amine linkages, and amide linkages.

24. The conjugate of claim 1, wherein the PEG is linear.

25. The conjugate of claim 1, wherein the PEG is branched.

26. A pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the conjugate of claim 1 and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition of claim 26, wherein said composition is stabilized by lyophilization and dissolves promptly upon reconstitution to provide solutions suitable for parenteral administration.

28. The conjugate of claim 11, wherein said uricase is truncated at said amino terminus by deleting at least the first six amino acids from said amino terminus.

29. The conjugate of claim 11, wherein said uricase is truncated at said carboxyl terminus by deleting at least the last three amino acids from said carboxyl terminus.

30. The conjugate of claim 11, wherein said uricase is truncated at said amino terminus and at said carboxyl terminus, by deleting at least the first six amino acids from said amino terminus and by deleting at least the last three amino acids from said carboxyl terminus.

31. The conjugate of claim 11, wherein said uricase is truncated at said amino terminus by deleting the first six amino acids from said amino terminus.

32. The conjugate of claim 11, wherein said uricase is truncated at said carboxyl terminus by deleting the last three amino acids from said carboxyl terminus.

33. The conjugate of claim 11, wherein said uricase is truncated at said amino terminus and at said carboxyl terminus, by deleting the first six amino acids from said amino terminus and by deleting the last three amino acids from said carboxyl terminus.